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TRANSLATION OF EUROPEAN PATENT (UK) UNDER SECTION 77(6) (a)

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in the name of HOECHST AKTIENGESELLSCHAFT

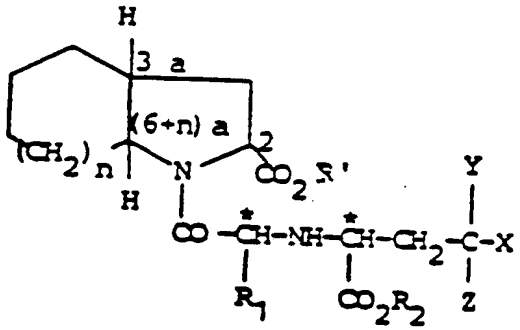
Signed this 15th day of December 1989

A. J. SPARROW

EP-A 0,037,231 discloses octahydroindole-2-carboxylic acid derivatives with the cis,endo configuration, diastereomer mixtures containing the latter, processes for the preparation thereof and the use thereof as inhibitors of angiotensin converting enzyme (ACE).

New bicyclic amino acid derivatives which strongly inhibit ACE and have a long-lasting and powerful hypotensive action have been found.

The present invention therefore relates to new derivatives of the bicyclic amino acids of the formula I



I

in which the hydrogen atoms on the bridgehead carbon atoms 3a and (6 + n)a have the cis or trans configuration relative to one another, wherein, in the case of the cis configuration, the carboxyl group on carbon atom 2 is oriented exo to the bicyclic ring system and wherein

n denotes 0, 1 or 2,

R_1 denotes hydrogen, (C_1-C_6)-alkyl which can optionally be substituted by amino, (C_1-C_4)-acylamino or benzoylamino, (C_2-C_6)-alkenyl, (C_5-C_9)-cycloalkyl, (C_5-C_9)-cycloalkenyl, (C_5-C_7)-cycloalkyl-(C_1-C_4)-alkyl, aryl or partially hydrogenated aryl, which can, in each case, be substituted by (C_1-C_2)-alkyl, (C_1-C_2)-alkoxy or halogen, aryl-(C_1-C_4)-alkyl, the aryl radical of which can be substituted as defined previously, a monocyclic or bicyclic heterocyclic radical having 5 to 7 or 8 to 10 ring atoms respectively, of which 1 to 2 ring atoms are sulfur or oxygen atoms and/or of which 1 to 4 ring atoms are

nitrogen atoms, or a side chain of a naturally occurring amino acid,

R_2 denotes hydrogen, (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl or aryl-(C_1-C_4)-alkyl,

R' denotes hydrogen, benzyl or tert.-butyl,

Y denotes hydrogen or hydroxyl,

Z denotes hydrogen or

Y and Z together denote oxygen,

X denotes (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl, (C_5-C_9)-cycloalkyl, aryl which can be mono-, di- or tri-substituted by (C_1-C_4)-alkyl, (C_1-C_4)-alkoxy, hydroxyl, halogen, nitro, amino, (C_1-C_4)-alkylamino, di-(C_1-C_4)-alkylamino or methylenedioxy, or indol-3-yl, and aryl denotes phenyl or naphthyl, and the physiologically acceptable salts thereof, excluding compounds of the formula I in which the hydrogen atoms on the bridgehead carbon atoms 3a and (6+n)a have the trans configuration relative to one another and wherein

R_1 denotes methyl,

R_2 denotes hydrogen, (C_1-C_4)-alkyl or benzyl,

R' denotes hydrogen and

X denotes phenyl and

n, Y and Z are as defined above, as well as the salts thereof.

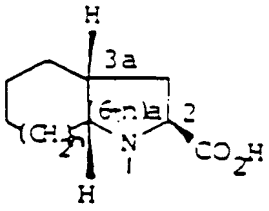
Particularly suitable salts are alkali metal and alkaline earth metal salts, salts with physiologically tolerated amines and salts with inorganic or organic acids such as, for example, HCl, HBr, H_2SO_4, maleic acid and fumaric acid.

In this context and in the following text, aryl is to be understood as meaning phenyl or naphthyl. Alkyl can be straight-chain or branched.

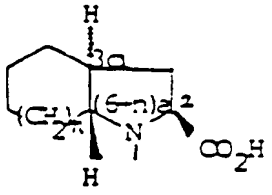
In the case of the trans configuration of the H atoms on C-3a and C-(6+n)a, there are two possible configurations of the bicycle, and these are the 2β, $3a\alpha$, $(6+n)a\beta$ configuration (part-formula Ib) and the 2β, $3a\beta$, $(6+n)a\alpha$

configuration (part-formula Ic), while in the case of the cis configuration of the H atoms, the carboxyl group must be oriented in the exo-position (= β-position).

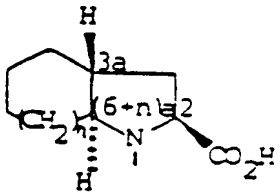
The exo-position (= β-position) of the carboxyl group on C-2 is defined so that the carboxyl group is oriented in the direction of the relevant hydrogen atoms, i.e. faces away from the concave side of the bicycle, for example corresponding to part-formula Ia. (For the definition of α and β, cf. Fieser and Fieser, Steroids, page 2, 1961).



Ia



Ib



Ic

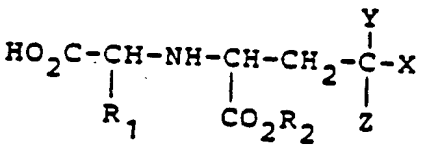
Compounds of the formula I have chiral carbon atoms in positions C-2, C-3a, C-(6+n)a, and in the carbon atoms labeled with an asterisk in the side chain. The invention relates to both the R and also the S configurations at all centers. The compounds of the formula I can thus be in the form of optical isomers, diastereomers, racemates or mixtures thereof. Compounds of the formula I are preferred in which the carbon atom 2 in the bicyclic ring system and the carbon atoms labeled with an asterisk in the side chain have the S configuration.

Preferred compounds of the formula I are those in which
R_1 denotes hydrogen, (C_1-C_3)-alkyl, (C_2-C_3)-alkenyl, benzyl or 4-aminobutyl,
R_2 denotes hydrogen, (C_1-C_4)-alkyl or benzyl and
X denotes phenyl which can be mono- or di-substituted or, in the case of methoxy, tri-substituted by (C_1-C_2)-alkyl, (C_1-C_2)-alkoxy, hydroxyl, fluorine, chlorine, bromine, amino, (C_1-C_4)-alkylamino, di-(C_1-C_4)-alkylamino, nitro or methylenedioxy.

Compounds of the formula I are particularly preferred in which R_1 denotes methyl and X denotes phenyl and in which R_2 denotes hydrogen or ethyl.

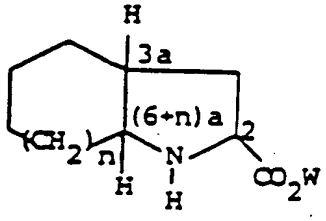
Compounds of the formula I to be emphasized are
N-(1S-carboethoxy-3-phenyl-propyl)-S-alanyl-2S,3aR,6aR-octahydrocyclopenta[b]pyrrole-2-carboxylic acid,
N-(1S-carboxy-3-phenyl-propyl)-S-alanyl-2S,3aR,7aR-octahydroindole-2-carboxylic acid and
N-(1S-carboxy-3-phenyl-propyl)-S-alanyl-2S,3aR,6aR-octahydrocyclopenta[b]pyrrole-2-carboxylic acid,
but especially
N-(1S-carboethoxy-3-phenyl-propyl)-S-alanyl-2S,3aR,7aR-octahydroindole-2-carboxylic acid.

The invention further relates to processes for the preparation of the compounds of the formula I. One process variant comprises reacting, by methods for amide formation known in peptide chemistry, a compound of the formula II



II

wherein R_1, R_2, X, Y and Z have the meanings as in formula I, with a compound of the formula III

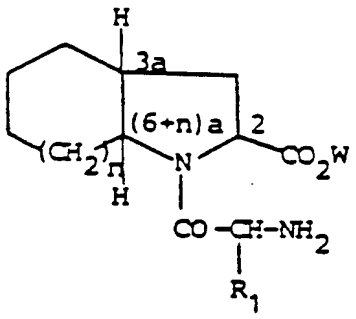


III

in which the hydrogen atoms on the carbon atoms 3 a and (6+n)a have the cis or trans configuration relative to one another, wherein, in the case of the cis configuration, the group $-CO_2W$ is oriented exo to the bicyclic ring system and wherein
n denotes 0, 1 or 2 and
W denotes a radical which can be cleaved off by

hydrogenolysis or by acid, in particular a benzyl or a tert.-butyl radical, and subsequently cleaving off, if appropriate, the radical W by catalytic hydrogenation or acid treatment and, if appropriate, also cleaving off the radical R_2 by additional acid or base treatment, the free carboxylic acids being obtained in each case.

Further synthetic processes for the preparation of the compounds of the formula I, in which Y and Z together denote oxygen, comprise reacting in a known manner in a Michael reaction (Organikum, 6th edition, page 492, 1967) a compound of the formula IV



IV

in which the hydrogen atoms on the carbon atoms 3a and (6+n)a have the cis or trans configuration relative to one another, wherein, in the case of the cis configuration, the group $-CO_2W$ is oriented exo to the bicyclic ring system, and wherein n and R_1 have the meanings as in formula I and W has the meaning as in formula III, with a compound of the formula V

$$R_2O_2C-CH=CH-CO-X \qquad V$$

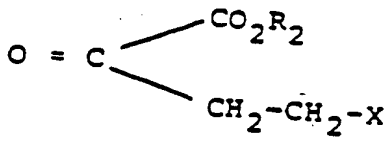
wherein R_2 and X have the meanings as in formula I, and subsequently cleaving off, if appropriate, the radical W and, if appropriate, the radical R_2 as described above, or comprise reacting in a known manner in a Mannich reaction (Bull. Soc. Chim. France 1973, page 625) a compound of the abovementioned formula IV with a compound of the general formula VI, wherein R_2 has the meaning as in formula I, and with a compound of the general formula VII

$OHC-CO_2R_2$ VI

$X-CO-CH_3$ VII

wherein X has the meaning as in formula I, and subsequently cleaving off, if appropriate, the radical W and, if appropriate, the radical R_2 as described above to form the free carboxyl groups.

Furthermore, compounds of the formula I with Y and Z being hydrogen can also be prepared in such a manner that a compound of the abovementioned formula IV is reacted in accordance with the procedure described in J. Amer. Chem. Soc. 93 2897 (1971) with a compound of the formula VIII

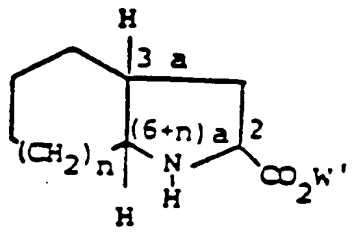


VIII

wherein R_2 and X have the meanings as in formula I, and the Schiff's bases obtained are reduced and subsequently, if appropriate, the radical W and, if appropriate, the radical R_2 are cleaved off as described above to form the free carboxyl groups, or that a compound of the formula I, in which Y and Z together denote oxygen, obtained according to the above procedures is reduced catalytically with hydrogen. The reduction of the Schiff's bases can be carried out catalytically, electrolytically or with reducing agents, such as, for example, sodium borohydride or sodium cyanoborohydride.

Compounds of the formula I with Y being hydroxyl and Z being hydrogen can also be obtained, for example, by reduction of a compound I with Y and Z together being oxygen obtained according to the above procedures. This reduction can be carried out catalytically with hydrogen or with another reducing agent, such as, for example, sodium borohydride.

The invention also relates to compounds of the formula III'

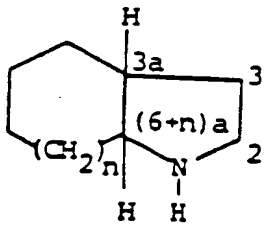


III'

in which the hydrogen atoms on the carbon atoms 3a and (6+n)a have the cis configuration relative to one another and the group $-CO_2W'$ on carbon atom 2 is oriented exo to the bicyclic ring system and wherein
n denotes 0, 1 or 2 and
W' denotes hydrogen, (C_1-C_{18})-alkyl or (C_7-C_{10})-aralkyl.

The preferred compounds are those of the formula III', wherein W' has the preferred meaning of W in the formula III and additionally denotes hydrogen. According to the invention, these compounds serve as starting materials for the synthesis of compounds of the formula I and can be prepared according to the invention by the following procedures.

One synthetic variant starts with a compound of the formula IX



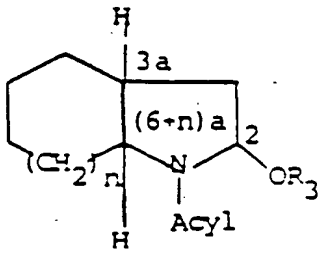
IX

wherein the hydrogen atoms on the carbon atoms 3a and (6+n)a have the cis configuration relative to one another and wherein n denotes the number 0, 1 or 2.

Compounds of the formula IX with n = 0 are known from Booth et al., J. Chem. Soc. 1959, page 1050, those with

n = 1 are known from King et al., J. Chem. Soc. 1953, pages 250 and 253 and those with n = 2 are known from Ayerst et al., J. Chem. Soc. 1960, page 3445.

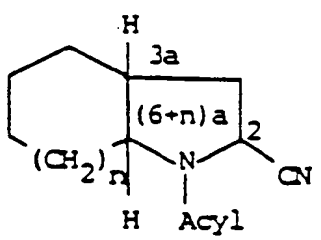
These compounds of the formula IX are acylated in a known manner, an aliphatic or aromatic acyl radical, preferably an acetyl or benzoyl radical, being bonded to the nitrogen atom, and the N-acylated compounds obtained are anodically oxidized (in analogy with Liebigs Ann. Chem. 1978 page 1719) in an aliphatic alcohol, preferably an alkanol having 1 to 4 carbon atoms, in particular methanol, in the presence of a conducting salt, preferably at temperatures in the range from 0° to 40°C with formation of a compound of the formula X, wherein n denotes 0, 1 or 2 and



X

R_3 denotes (C_1-C_4)-alkyl.

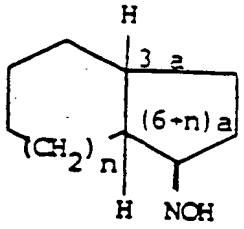
The compound of the general formula X obtained is reacted with trimethylsilyl cyanide in accordance with Tetrahedron Letters 1981, page 141 in an aprotic organic solvent, such as, for example, in a hydrocarbon, halogenated hydrocarbon, in ether or in THF at temperatures in the range from -60°C to +20°C, preferably -40°C to ±0°C in the presence of a Lewis acid, such as, for example, $ZnCl_2$, $SnCl_2$, $SnCl_4$, $TiCl_4$ or BF_3 etherate, preferably BF_3 etherate, and the compound of the formula XI obtained



XI

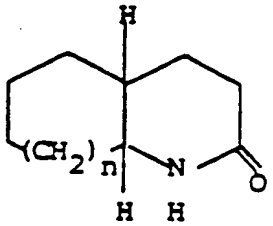
wherein the hydrogen atoms on the carbon atoms 3a and (6+n)a have the cis configuration relative to one another, wherein the group -CN is oriented exo to the bicyclic ring system and wherein n has the abovementioned meaning, after purification and separation from by-products by means of recrystallization or column chromatography, is hydrolyzed by the action of acids or bases in a known manner to give a compound of the formula III' with W' = hydrogen, and the latter is esterified if appropriate. In particular, in the acid hydrolysis of the nitrile group, HCl or HBr is used as the acid. In this instance as in the following text, the esterification is carried out by the procedures usual in amino acid chemistry.

Compounds of the general formula III' can also be prepared by converting, in a Beckmann rearrangement analogous to Helv. Chim. Acta 46, 1190 (1963), a compound of the formula XII



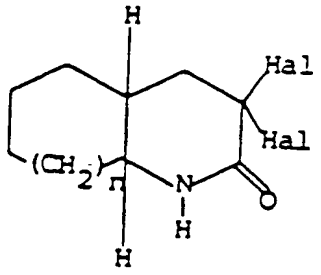
XII

wherein the hydrogen atoms on the carbon atoms 3a and (6+n)a have the cis configuration and n has the abovementioned meaning, into a compound of the formula XIII, wherein n has the abovementioned meaning



XIII

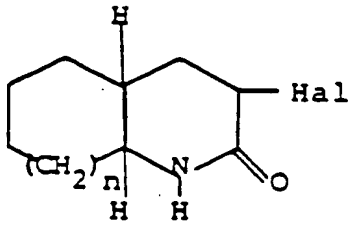
and halogenating the latter to give a compound of the formula XIV



XIV

wherein n has the abovementioned meaning and Hal denotes a halogen atom, preferably chlorine or bromine. Examples of suitable halogenating agents are halides of inorganic acid, such as PCl_5, SO_2Cl_2, $POCl_3$, $SOCl_2$, PBr_3 or halogens, such as bromine. It is advantageous to use PCl_5 or $POCl_3$ combined with SO_2Cl_2. The intermediate initially formed is an imide halide, which, with the halogenating agents mentioned and subsequent hydrolysis under basic conditions, preferably with aqueous alkali metal carbonate, reacts further to give a compound of the formula XIV.

The compounds of the formula XIV are subsequently reduced catalytically in a polar protic solvent, such as, for example, an alcohol, preferably ethanol, or a carboxylic acid, such as, for example, acetic acid, with the addition of an acid acceptor, such as, for example, sodium acetate or triethylamine, to give a compound of the formula XV



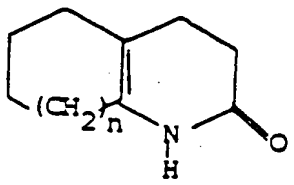
XV

wherein n and Hal have the abovementioned meanings. Examples of suitable catalysts are Raney nickel or palladium or platinum on animal charcoal. Compounds of

the formula XV can also be prepared directly by halogenation of compounds of the formula XIII using smaller amounts of the abovementioned halogenating agents.

Compounds of the formula XV are converted, in accordance with the known Favorskii reaction in the presence of a base, into a compound of the formula III' with W' = hydrogen, and the latter is esterified if appropriate. The abovementioned Favorskii reaction is carried out in an alcoholic solvent, such as methanol, ethanol or tert.-butanol, or in water or in mixtures thereof at temperatures in the range from 20° to 140°C, preferably between 60° and 100°C. Bases which are advantageously employed are alkali metal or alkaline earth metal hydroxides, such as sodium, potassium or barium hydroxide or alkali metal alcoholates, such as, for example, sodium methylate or potassium tert.-butanolate.

Furthermore, the compounds of the formula III', wherein the hydrogen atoms on the carbon atoms 3a and (6+n)a have the cis configuration, can be prepared from the compound of the formula XVI, wherein n denotes 0, 1 or 2,

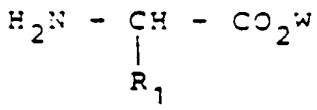


XVI

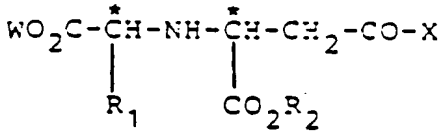
by reducing the latter by means of platinum oxide/acetic acid in accordance with Ann. Chim. 62, 200 (1972) to give a compound of the abovementioned formula XIII and reacting the latter in accordance with the procedures described above. Compounds of the formula XVI are known from J. Org. Chem. 29, 2780 (1964).

The compounds of the formula III' may be converted, if appropriate by methods such as are described, for example, in Houben-Weyl, Vol. VIII (1952), into the C_1-C_{18}-alkyl or C_7-C_{10}-aralkyl ester.

The compounds of the formula II with Y and Z = hydrogen, R_1 = methyl and R_2 = methyl or ethyl and X = phenyl which are used as starting materials for the preparation of the compounds of the formula I are known (European Patent Application No. 37,231). The compounds of the formula II can be prepared by various procedures. One synthetic variant starts from a ketone of the abovementioned formula VII, which is reacted by known procedures in a Mannich reaction with a compound of the abovementioned formula VI together with amino acid esters of the formula XXII



XXII



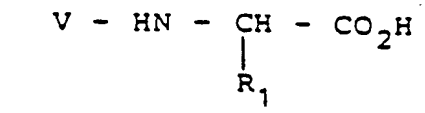
XXIII

wherein R_1 and W have the abovementioned meanings, to give a compound of the formula XXIII, wherein R_1, R_2, X and W have the abovementioned meanings, with the proviso that in the case where W denotes a radical which can be split off by hydrogenolysis, in particular benzyl, R_2 may not have the meaning of W. If the radical W is split off by hydrogenolysis using, for example, palladium, compounds of the formula II with Y and Z = hydrogen are obtained. If the radical W is split off with acids, such as, for example, trifluoroacetic acid or hydrochloric acid in an inert organic solvent, such as, for example, dioxane, compounds of the formula II with Y and Z together = oxygen are obtained.

Compounds of the formula XXIII can also be obtained by Michael addition of a compound of the abovementioned formula V with a compound of the abovementioned formula XXII by known procedures. Preferentially, this process is suitable for the preparation of those compounds of the formula XXIII in which R_1 denotes methyl, R_2 denotes ethyl and X denotes aryl.

The compounds of the formula XXIII are obtained as mixtures of diastereomers. Preferred diastereomers of the formula XXIII are those in which the chiral carbon atoms labeled with an asterisk each have the S configuration. These can be separated out by recrystallization or by chromatography, for example on silica gel. The configurations of the chiral carbon atoms are maintained during the subsequent cleavage off of the radical W.

The compounds of the abovementioned formula IV used as starting materials for the preparation of the compounds of the formula I are obtained by known procedures from compounds of the abovementioned formula III by reaction with an N-protected 2-amino carboxylic acid of the formula XXIV



XXIV

wherein V is a protective group and R_1 has the abovementioned meaning. Examples of suitable protective groups V, which are cleaved off again after completion of the reaction, are the groups benzyloxycarbonyl or tert.-butoxycarbonyl.

The reaction of a compound of the formula II with a compound of the formula III to prepare a compound of the formula I is carried out by a condensation reaction known in peptide chemistry, the condensing agent added being, for example, dicyclohexylcarbodiimide and 1-hydroxybenzotriazole. In the subsequent removal of the radical W by hydrogenolysis, the catalyst used is preferably palladium, while the acids employed for the acid removal of the radical W are preferably trifluoroacetic acid or hydrogen chloride.

In the reactions described above for the preparation of the compounds of the formulae III', IV and I, the configurations at the bridgehead carbon atoms 3a and (6+n)a in the intermediate products are retained in each case.

If, for the preparation of the compounds of the formulae III', IV or I, corresponding starting materials having the cis configuration of the hydrogen atoms on C-3a and C-(6+n)a are employed, the exo (or β) isomers are obtained almost exclusively, and small proportions of the isomers can be removed by recrystallization or by chromatography.

The compounds of the formula III' obtained according to the procedures described above are produced as racemic mixtures and can be employed as such in the further syntheses described above. However, they can also be employed as the pure enantiomers after separation of the racemates into the optical antipodes by customary methods, for example, via salt formation with optically active bases or acids.

If the compounds of the formula I are produced as racemates, these can also be resolved into their enantiomers by customary methods, such as, for example, via salt formation with optically active bases or acids.

The compounds of the formula I according to the invention are in the form of internal salts. Since they are amphoteric compounds, they can form salts with acids or bases. These salts are prepared in a customary manner by reaction with one equivalent of acid or base.

The compounds of the formula I and their salts have a long-lasting and powerful hypotensive action. They are strong inhibitors of the angiotensin converting enzyme (ACE inhibitors). They can be employed to control high blood pressure of various etiologies. It is also possible to combine them with other compounds having hypotensive, vasodilator or diuretic activity. Typical representatives of these classes of active compounds are described, for example, in Erhardt-Ruschig, Arzneimittel (Drugs), 2nd edition, Weinheim, 1972. They can be used intravenously, subcutaneously or perorally.

The dosage on oral administration is 1-100 mg, preferably 1-40 mg, for a single dose for an adult patient of normal weight. This can also be increased in severe cases, since no toxic properties have been observed hitherto. A decrease in the dose is also possible and is particularly appropriate when diuretics are administered concurrently.

The compounds according to the invention can be administered orally or parenterally in an appropriate pharmaceutical formulation. For a form for oral use, the active compounds are mixed with the additives customary for this purpose, such as vehicles, stabilizers or inert diluents and converted by customary methods into suitable forms for administration, such as tablets, coated tablets, hard capsules, aqueous, alcoholic or oily suspensions or aqueous, alcoholic or oily solutions. Inert vehicles which can be used are, for example, gum arabic, magnesium carbonate, potassium phosphate, lactose, glucose or starch, particularly corn starch. In this context, the formulation can either be as dry or as moist granules. Examples of suitable oily vehicles or solvents are plant and animal oils, such as sunflower oil or cod-liver oil.

For subcutaneous or intravenous administration, the active compounds or their physiologically tolerated salts are converted into solutions, suspensions or emulsions, if desired together with the substances customary for this purpose such as solubilizers, emulsifiers or other auxiliaries. Examples of suitable solvents for the new active compounds and the corresponding physiologically tolerated salts are: water, physiological saline solutions or alcohols, for example ethanol, propanediol or glycerol, additionally also sugar solutions, such as glucose or mannitol solutions, or also a mixture of the various solvents mentioned.

The extremely high activity of the compounds according to formula I is demonstrated by the pharmacological data in

the following table:

Intraduodenal administration to the anesthetized rat, 50% inhibition of the pressor reaction induced by 310 ng of angiotensin I 30 min after administration in the dose....= ED_{50}:

Table

(Hydrogen atoms on C-3a and C-(6+n)a in formula I have the cis configuration)

n	X	Y	Z	R_2	R_1	ED_{50} (µg/kg)
0		H	H	C_2H_5	CH_3	40
0		H	H	H	CH_3	700
1		H	H	C_2H_5	CH_3	50
1		H	H	H	CH_3	600
2		H	H	C_2H_5	CH_3	230
2		H	H	H	CH_3	840
1		- O -		C_2H_5	CH_3	390

The symbols n, X, Y, Z, R_1 and R_2 relate to the compounds of the formula I.

The following examples serve to illustrate the invention but do not restrict it to the compounds mentioned as representatives:

Example 1

2β,3aβ,7aβ-Octahydroindole-2-carboxylic acid

a) N-Acetyl-3aβ,7aβ-octahydroindole

3.5 g of platinum oxide were added to a solution of 77 g of indole in 700 ml of glacial acetic acid. The compound was initially hydrogenated under 100 atmospheres at 20 to 25°C for 16 hours and then under atmospheric pressure at 20 to 25°C until the uptake of hydrogen was complete. The catalyst was filtered off with suction and the solvent was distilled off in vacuo. The residue was taken up in water and made alkaline with saturated potassium carbonate solution. After saturation with sodium chloride, the aqueous phase was extracted four times with methylene chloride and the organic phase was dried and evaporated.

The residue was taken up in 250 ml of pyridine, 93 ml of acetic anhydride were added and the mixture was allowed to react at 20 to 25°C for 12 hours. After distilling off the pyridine, water was added to the residue and the mixture was made alkaline with concentrated aqueous sodium hydroxide. The aqueous phase was extracted with methylene chloride, the organic phase obtained was washed with 2 N hydrochloric acid and then with water. After drying and concentrating the solution, the residue was distilled.

Yield: 85 g; b.p.: 91 to 95°C/0.2 mm Hg.

b) N-Acetyl-2-methoxy-3aβ,7aβ-octahydroindole

54 g of N-acetyl-3aβ,7aβ-octahydroindole were anodically oxidized in methanol, with the addition of tetramethylammonium tetrafluoroborate, according to the details in Liebigs Ann. Chem. 1978, page 1719. The solvent was distilled off and the residue was filtered

through 500 g of silica gel by means of ethyl acetate. 53.6 g of the abovementioned product were obtained from the ethyl acetate solution after evaporation. R_f value (thin-layer chromatogram): 0.33 (silica gel, ethyl acetate).

c) N-Acetyl-2β,3aβ,7aβ-octahydroindole-2-carbonitrile

25 g of trimethylsilyl cyanide in 50 ml of methylene chloride were added dropwise to a solution of 49.8 g of N-acetyl-2-methoxy-3aβ,7aβ-octahydroindole in 250 ml of methylene chloride at -40°C. Subsequently, 35.9 g of boron trifluoride etherate were added dropwise so that the temperature of the reaction mixture did not exceed -20°C. After 2 hours of reaction at -20°C, the temperature was slowly raised to 0°C, the mixture was stirred overnight at 0°C and then for one hour at 20 to 25°C. Water was added to the mixture and this was stirred for 10 min. The aqueous phase was extracted three times with methylene chloride. The combined organic extracts were dried, concentrated and the residue was triturated with diisopropyl ether.

Yield: 47 g; m.p. 128° to 130°C.

d) 2β,3aβ,7aβ-Octahydroindole-2-carboxylic acid

10 g of N-acetyl-2β,3aβ,7aβ-octahydroindole-2-carbonitrile in 30 ml of concentrated hydrogen bromide were heated to boiling for 2 hours. After distilling off the hydrogen bromide, the residue was stirred with a little acetone and filtered off with suction.

An aqueous solution of the product was adjusted to a pH of 6.0 with a weakly basic ion exchanger. After filtration, the solution was evaporated and the residue was filtered through silica gel with a mixture of methylene chloride, methanol, glacial acetic acid

and water in the ratio 20:10:0.5:0.5. The eluate was concentrated and the residue was triturated with diisopropyl ether.
Yield: 7.6 g

^{1}H NMR spectrum*: 1.0-2.5 (m, 11H); 3.4-3.9 (m, 1H); 4.0-4.5 (m, 1H); 7.5-8.3 (broad s, exchangeable with D_2O)

When the process was carried out in analogy to the procedures described under Example 1, the compounds mentioned under Example 2 and Example 3 in the following text were obtained:

Example 2

2β,3aβ,6aβ-Octahydrocyclopenta[b]pyrrole-2-carboxylic acid

a) N-Acetyl-cis-octahydrocyclopenta[b]pyrrole

^{1}H NMR data: 1.0 to 2.3 (m, 9H);
2.0 (d, 3H);
3.3 to 4.2 (m, 3H)

b) N-Acetyl-2-methoxy-cis-octahydrocyclopenta[b]pyrrole

^{1}H NMR data: 0.9 to 2.6 (m, 9H);
2.1 (s, 3H);
3.3 (s, 3H);
3.8 - 4.3 (m, 1H);
4.7 - 5.5 (m, 1H).

c) N-Acetyl-2-cyano-cis-octahydrocyclopenta[b]pyrrole

*Here and in the following text, the ^{1}H NMR data were obtained in $CDCl_3$ and are reported in ppm.

^{1}H NMR data: 1.0 - 3.0 (m, 9H);
2.1 (d, 3H);
3.5 - 4.1 (m, 1H);
4.4 - 4.7 (m, 1H).

d) 2β,3aβ,6aβ-Octahydrocyclopenta[b]pyrrole-2-carboxylic acid

^{1}H NMR data: 1.0 - 2.3 (m, 9H);
3.5 - 3.9 (m, 1H);
4.0 - 4.6 (m, 1H);
7.7 - 8.4 (broad s, exchangeable with D_2O)

Example 3

2β,3aβ,8aβ-Decahydrocyclohepta[b]pyrrole-2-carboxylic acid

a) N-Acetyl-cis-decahydrocyclohepta[b]pyrrole

^{1}H NMR data: 0.9 - 2.5 (m, 13H);
2.1 (s, 3H);
3.1 - 4.1 (m, 3H).

b) N-Acetyl-2-methoxy-cis-decahydrocyclohepta[b]pyrrole

^{1}H NMR data: 0.9 - 2.7 (m, 13H);
2.1 (s, 3H);
3.2 (s, 3H);
3.7 - 4.2 (m, 1H);
4.7 - 5.3 (m, 1H)

c) N-Acetyl-2-cyano-cis-decahydrocyclohepta[b]pyrrole

^{1}H NMR data: 0.9 - 3.1 (m, 13H);
2.1 (s, 3H);
3.5 - 4.1 (m, 1H);
4.3 - 4.7 (m, 1H)

d) 2β,3aβ,8aβ-Decahydrocylohepta[b]pyrrole-2-carboxylic acid (sic)

^{1}H NMR data: 0.8 - 2.4 (m, 13H);
3.5 - 3.9 (m, 1H);
4.1 - 4.6 (m, 1H);
7.6 - 8.3 (broad s, exchangeable with D_2O)

Example 4

2β,3aβ,7aβ-Octahydroindole-2-carboxylic acid

a) 3,4,5,6,7,8-Hexahydro-1H-quinolin-2-one

392 g of cyclohexanone and 212 g of acrylonitrile together with 20 g of cyclohexylamine, 4 g of glacial acetic acid and 0.4 g of hydroquinone were heated under reflux for 4 hours up to a final temperature of 200°C. After distillation at 100 to 150°C/0.5 mm Hg, the residue remaining, which contained the desired product, was recrystallized from n-hexane.

The distillate was heated with 10 ml of 10% strength acetic acid at 200°C for 2 days. After cooling down, further product was obtained which was crystallized from methanol/water.

A total of 460 g of the title compound was obtained, m.p.: 143 - 144°C.

b) Cis-octahydro-1H-quinolin-2-one

One gram of platinum(IV) oxide was added to a solution of 80 g of 3,4,5,6,7,8-hexahydro-1H-quinolin-2-one and this was hydrogenated at 20 to 25°C under atmospheric pressure. After filtration of the reaction solution, it was evaporated and the residue was fractionally crystallized from n-hexane. 35 g of cis-octahydro-1H-quinolin-2-one having a melting point of 123 to 126°C

were obtained.

c) 3,3-Dichloro-cis-octahydro-1H-quinolin-2-one

28.8 g of phosphorus pentachloride were added to a solution of 23 g of cis-octahydro-1H-quinolin-2-one in 350 ml of anhydrous chloroform. To this were added dropwise 43.1 g of sulfuryl chloride in 45 ml of anhydrous chloroform at 20 to 30°C within 30 min and the reaction mixture was stirred at the boiling point for 5 hours. After allowing to stand overnight, the mixture was neutralized with aqueous potassium carbonate cooled to 0°C. The aqueous phase was extracted twice with methylene chloride. The combined organic phases were dried over sodium sulfate and concentrated. The residue was recrystallized from ethanol with the addition of active charcoal. 32 g of pale yellow crystals, having a melting point of 176 to 177°C, were obtained.

d) 3-Chloro-cis-octahydro-1H-quinolin-2-one

15.9 g of 3,3-dichloro-cis-octahydro-1H-quinolin-2-one in one liter of ethanol, with the addition of 10 ml of triethylamine and Raney nickel, were hydrogenated at 20 to 25°C under atmospheric pressure until one mole-equivalent of hydrogen had been taken up. After filtration, the solution was evaporated, the residue was taken up in ethyl acetate, the solution was extracted twice with water and dried over sodium sulfate. After removal of the solvent, the product was triturated with diisopropyl ether and filtered off with suction. Colorless crystals, having a melting point of 185°C, were obtained.

e) 2β,3aβ,7aβ-Octahydroindole-2-carboxylic acid

3.75 g of 3-chloro-cis-octahydro-1H-quinolin-2-one were added to a boiling solution of 6.63 g of barium

hydroxide octahydrate in 120 ml of water. After heating under reflux for 3.5 hours, 0.9 ml of concentrated sulfuric acid was added to the reaction mixture and this was heated to boiling for a further hour and then allowed to stand overnight.

The precipitate was filtered off with suction and the filtrate was adjusted to a pH of 6.5 with 1 N sodium hydroxide and evaporated to dryness. The residue was extracted with boiling ethanol, concentrated and induced to crystallize.
Yield: 3.1 g

The compounds 2β-cis-octahydrocyclopenta[b]pyrrole-2-carboxylic acid (corresponds to the compound from Example 2 d) and 2β,3aβ,8aβ-decahydrocyclohepta[b]-pyrrole-2-carboxylic acid (corresponds to the compound in Example 3 d) may also be prepared in a manner analogous to that described in Example 4.

Example 5

Benzyl 2β,3aβ,7aβ-octahydroindole-2-carboxylate hydrochloride

3 ml of thionyl chloride were added dropwise to 25 ml of benzyl alcohol. 3 g of 2β,3aβ,7aβ-octahydroindole-2-carboxylic acid hydrochloride were added to this mixture. The reaction mixture was allowed to stand at 5°C for 2 days, after which a clear solution had formed. After evaporation, diisopropyl ether was added to the residue obtained and this was filtered off with suction. 3.8 g of the title compound, having a melting point of 150°C (with decomposition), were obtained.

The following ester compounds in Examples 6 and 7 may be prepared in a manner analogous to that described in Example 5:

Example 6

Benzyl 2β,3aβ,6aβ-octahydrocyclopenta[b]pyrrole-2-carboxylate hydrochloride

^{1}H NMR data: 1.0 - 2.3 (m, 9H);
3.4 - 3.9 (m, 1H);
4.1 - 4.6 (m, 1H);
5.1 (s, 2H);
7.2 (s, 5H).

Example 7

Benzyl 2β,3aβ,8aβ-decahydrocyclohepta[b]pyrrole-2-carboxylate hydrochloride

^{1}H NMR data: 0.9 - 2.3 (m, 13H);
3.5 - 3.9 (m, 1H);
4.2 - 4.7 (m, 1H);
5.2 (s, 2H);
7.2 (s, 5H).

Example 8

Tert.-butyl 2β,3aβ,7aβ-octahydroindole-2-carboxylate hydrochloride

10 ml of concentrated sulfuric acid and 50 g of isobutylene were added to a solution of 10 g of 2β,3aβ,7aβ-octahydroindole-2-carboxylic acid in 10 ml of dioxane cooled down to -10°C. The reaction mixture was slowly warmed to 20 to 25°C in an autoclave and stirred at this temperature for 20 hours.

The mixture was added to ice-cold 50% strength aqueous sodium hydroxide and extracted with methylene chloride. The combined organic phases were washed with water, dried with sodium sulfate and concentrated. The residue was

taken up in ether and the pH was adjusted to 2.0 to 3.0 by means of ethereal hydrogen chloride. The mixture was evaporated to dryness and the product was triturated with diisopropyl ether. 7.3 g of the title compound were obtained after filtering off with suction.

^{1}H NMR data: 1.0 - 2.5 (m, 11H);
1.3 (s, 9H);
3.4 - 3.9 (m, 1H);
4.0 - 4.5 (m, 1H).

The following ester compounds of Examples 9 and 10 can be prepared in analogy to the procedure described in Example 8:

Example 9

Tert.-butyl 2β,3aβ,6aβ-octahydrocyclopenta[b]pyrrole-2-carboxylate hydrochloride

^{1}H NMR data: 1.0 - 2.7 (m, 9H);
1.3 (s, 9H);
3.4 - 3.9 (m, 1H);
4.0 - 4.5 (m, 1H).

Example 10

Tert.-butyl 2β,3aβ,8aβ-decahydrocyclohepta[b]pyrrole-3-carboxylate hydrochloride

^{1}H NMR data: 0.8 - 2.9 (m, 13H);
1.3 (s, 9H);
3.4 - 3.9 (m, 1H);
4.0 - 4.5 (m, 1H).

Example 11

Benzyl N-(1S-carboethoxy-3-phenylpropyl)-S-alanyl-2S,3aR,7aR-octahydroindole-2-carboxylate (= diastereomer A 11) and benzyl N-(1S-carboethoxy-3-phenylpropyl)-S-alanyl-2R,3aS,7aS-octahydroindole-2-carboxylate (= diastereomer B 11)

2.5 g of N-(1S-carboethoxy-3-phenylpropyl)-S-alanine, 1.22 g of 1-hydroxybenzotriazole, 2.5 g of benzyl (d,l)-2β,3aβ,7aβ-octahydroindole-2-carboxylate hydrochloride, 1.25 ml of N-ethylmorpholine and 2 g of dicyclohexylcarbodiimide were added to 20 ml of dimethylformamide at 0°C.

The mixture was stirred at 0°C for 1 hour, then slowly warmed to room temperature and stirred at 20 to 25°C overnight.

25 ml of ethyl acetate were added to the reaction mixture and precipitated urea was filtered off with suction. After evaporation of the solution, the residue obtained was taken up in 50 ml of ether, the ethereal solution was washed with saturated aqueous sodium bicarbonate and water, dried and concentrated. A mixture of the abovementioned diastereomers A 11 and B 11 was obtained which was separated over silica gel using a mixture of cyclohexane and ethyl acetate (4:1).

R_f value for diastereomer A 11: 0.36
R_f value for diastereomer B 11: 0.34

The following compounds in Examples 12 to 16 were obtained in a procedure analogous to that described in Example 11:

Example 12

Tert.-butyl N-(1S-carboethoxy-3-phenylpropyl)-S-alanyl-2S,3aR,7aR-octahydroindole-2-carboxylate (= diastereomer A 12)

^{1}H NMR data: 1.25 (d+t, 6H);
1.35 (s, 9H);
1.3 - 3.6 (m, 18H);
4.2 (q, 2H);
4.4 (m, 1H);
7.3 (s, 5H).

Example 13

Benzyl N-(1S-carboethoxy-3-phenylpropyl)-S-alanyl-2S,3aR,6aR-octahydrocyclopenta[b]pyrrole-2-carboxylate (= diastereomer A 13)

^{1}H NMR data: 1.1 (d, 3H);
1.3 (t, 3H);
1.3 - 2.4 (m, 10H);
2.3 - 3.4 (m, 6H);
4.1 (q, 2H);
4.55 (d, 1H);
5.2 (s, 2H);
7.2 (s, 5H);
7.4 (s, 5H).

Example 14

Benzyl N-(1S-carboethoxy-3-phenylpropyl)-S-alanyl-2S,3aR,8aR-octahydrocyclohepta[b]pyrrole-2-carboxylate (= diastereomer A 14)

^{1}H NMR data: 1.2 (d + t, 6H);
1.3 - 2.4 (m, 14H);
2.3 - 3.4 (m, 6H);
4.2 (q, 2H);

4.6 (m, 1H);
5.2 (s, 2H);
7.25 (s, 5H);
7.4 (s, 5H).

Example 15

Tert.-butyl N-(1S-carboethoxy-3-phenylpropyl)-S-alanyl-2S,3aR,6aR-octahydrocyclopenta[b]pyrrole-2-carboxylate (= diastereomer A 15)

^{1}H NMR data: 1.1 (d, 3H);
1.3 (t, 3H);
1.3 - 2.4 (m, 10H);
1.4 (s, 9H);
2.3 - 3.4 (m, 6H);
4.2 (q, 2H);
4.6 (m, 1H);
7.2 (s, 5H).

Example 16

Tert.-butyl N-(1S-carboethoxy-3-phenylpropyl)-S-alanyl-2S,3aR,6aR-octahydrocyclohepta[b]pyrrole-2-carboxylate (= diastereomer A 16)

^{1}H NMR data: 1.1 (d, 3H);
1.3 (t, 3H);
1.4 (s, 9H);
1.4 - 2.5 (m, 14H);
2.3 - 3.4 (m, 6H);
4.1 (q, 2H);
4.7 (m, 1H);
7.3 (s, 5H).

Example 17

N-(1S-Carboethoxy-3-phenylpropyl)-S-alanyl-2S,3aR,7aR-octahydroindole-2-carboxylic acid hydrochloride

Method A:

0.7 g of diastereomer A 11 from Example 11 were hydrogenated in 25 ml of ethanol with 100 ml of palladium-animal charcoal (10%) at 20 to 25°C under atmospheric pressure. After removal of the catalyst, the solution was treated with 0.5 N ethanolic hydrogen chloride until the reaction was acid. The solution was concentrated in vacuo and the residue was triturated with diisopropyl ether. 400 mg of the title compound, having a melting point of 198 to 200°C, were obtained.

^{1}H NMR data of the free base: 1.0 - 3.0 (m, 19H);
3.0 - 3.3 (t, 1H);
3.3 - 3.9 (m, 3H);
3.9 - 4.4 (q, 2H);
4.4 - 4.7 (broad s, 4H);
7.2 (s, 5H).

Method B:

A solution of 0.8 g of diastereomer A 12 from Example 12 in 5 ml of methylene chloride was saturated with dry hydrogen chloride gas and allowed to stand at 20 to 25°C for 16 hours. The solution was concentrated in vacuo, the residue was triturated with diisopropyl ether and filtered off with suction.
Yield: 550 mg.

Example 18

N-(1S-Carboethoxy-3-phenylpropyl)-S-alanyl-2S,3aR,6aR-octahydrocyclopenta[b]pyrrole-2-carboxylic acid hydrochloride

This compound was obtained from the diastereomer A 13 in

Example 13 in a procedure analogous to method A in Example 17.

^{1}H NMR data: 1.2 (d, 3H);
1.3 (t, 3H);
1.2 - 3.8 (m, 16H);
4.15 (q, 2H);
4.2 - 4.6 (m, 4H);
7.2 (s, 5H).

Example 19

N-(1S-Carboethoxy-3-phenylpropyl)-S-alanyl-2S,3aR,8aR-octahydrocyclopenta[b]pyrrole-2-carboxylic acid hydrochloride

This compound was obtained from the diastereomer A 14 in Example 14 in a procedure analogous to method A in Example 17.

^{1}H NMR data: 1.2 (d, 3H);
1.3 (t, 3H);
1.2 - 3.8 (m, 20H);
4.2 (q, 2H);
4.0 - 4.7 (m, 4H);
7.2 (s, 5H).

The compounds of Examples 18 and 19 can also be prepared from the diastereomers A 15 and A 16 respectively by the method B described in Example 17.

Example 20

N-(1S-Carboxy-3-phenylpropyl)-S-alanyl-2S,3aR,7aR-octahydroindole-2-carboxylic acid

Two equivalents of potassium hydroxide and a 10% excess of 4 N potassium hydroxide were added to a solution of 1 g of N-(1S-carboethoxy-3-phenylpropyl)-S-alanyl-

2S,3aR,7aR-octahydroindole-2-carboxylic acid hydrochloride in 10 ml of water. After stirring for 8 hours at 20 to 25°C, the reaction solution was adjusted to a pH of 4.0 with 2 N hydrochloric acid and concentrated in vacuo. The residue was taken up in ethyl acetate and precipitated salt was filtered off. The ethyl acetate solution was concentrated and the residue was triturated with diisopropyl ether and filtered off with suction.
Yield: 0.6 g

^{1}H NMR data: 1.2 (d, 3H);
1.2 - 3.8 (m, 18H);
4.0 - 4.6 (m, 4H);
7.2 (s, 5H).

Example 21

N-(1S-Carboxy-3-phenylpropyl)-S-alanyl-2S,3aR,6aR-octahydrocyclopenta[b]pyrrole-2-carboxylic acid

This compound was prepared from the compound in Example 18 in analogy to the process described in Example 20.

^{1}H NMR data: 1.2 (d, 3H);
1.2 - 3.8 (m, 16H);
4.05 - 4.7 (m, 4H);
7.2 (s, 5H).

Example 22

N-(1S-Carboxy-3-phenylpropyl)-S-alanyl-2S,3aR,8aR-decahydrocyclohepta[b]pyrrole-2-carboxylic acid

This compound was prepared from the compound in Example 19 in analogy to the process described in Example 20.

^{1}H NMR data: 1.2 (d, 3H);
1.3 - 3.9 (m, 20H);
4.0 - 4.7 (m, 4H);

7.2 (s, 5H).

Example 23

Tert.-butyl N-(1S-carboethoxy-3-phenyl-3-oxopropyl)-S-alanyl-2β,3aβ,7aβ-octahydroindole-2-carboxylate

2.5 g of N-(1S-carboethoxy-3-phenyl-3-oxopropyl)-S-alanine, together with 1.2 g of 1-hydroxybenzotriazole, 2.5 g of tert.-butyl (d,l)2β,3aβ,7aβ-octahydroindole-2-carboxylate hydrochloride, 1.25 ml of N-ethylmorpholine and 2 g of dicyclohexylcarbodiimide, were added to 20 ml of dimethylformamide. The mixture was stirred at 0°C for 1 hour and then at 20 to 25°C for 12 hours.

The reaction solution was diluted with 25 ml of ethyl acetate and precipitated urea was filtered off with suction. After concentration in vacuo, the residue obtained was taken up in ether, the ethereal solution was washed with saturated aqueous sodium bicarbonate and with water, dried and evaporated. 3 g of the title compound were obtained as a mixture of diastereomers.

^{1}H NMR data: 1.2 (s, 9H);
0.9 - 2.6 (m, 18H);
3.5 - 5.1 (m, 6H);
7.2 - 8.2 (m, 5H).

The mixture of diastereomers can be separated over silica gel into the optically pure compounds using cyclohexane/ethyl acetate as the eluent.

Examples 24 to 28

The following compounds of Examples 24 to 28 may be prepared in a procedure analogous to Example 23 using the appropriate bicyclic carboxylic acid ester compounds.

Example 24

Tert.-butyl N-(1S-carboethoxy-3-phenyl-3-oxopropyl)-S-alanyl-2β,3aβ,6aβ-octahydrocyclopenta[b]pyrrole-2-carboxylate

^{1}H NMR data: 1.2 (s, 9H);
0.9 - 2.5 (m, 16H);
3.5 - 5.1 (m, 6H);
7.2 - 8.2 (m, 5H).

Example 25

Tert.-butyl N-(1S-carboethoxy-3-phenyl-3-oxopropyl)-S-alanyl-2S,3aR,8aR-decahydrocyclohepta[b]pyrrole-2-carboxylate

^{1}H NMR data: 1.4 (s, 9H);
1.0 - 2.8 (m, 20H);
3.4 - 5.1 (m, 6H);
7.2 - 8.2 (m, 5H).

Example 26

Benzyl N-(1S-carboethoxy-3-phenyl-3-oxopropyl)-S-alanyl-2β,3aβ,7aβ-octahydroindole-2-carboxylate

^{1}H NMR data: 1.2 (d, 3H);
1.3 (t, 3H);
1.4 - 2.4 (m, 10H);
2.4 - 3.9 (m, 6H);
4.2 (q, 2H);
4.3 - 4.8 (m, 1H);
5.2 (s, 2H);
7.2 (s, 5H);
7.4 - 8.0 (m, 5H).

Example 27

Benzyl N-(1S-carboethoxy-3-phenyl-3-oxopropyl)-S-alanyl-2β,3aβ,6aβ-octahydrocyclopenta[b]pyrrole-2-carboxylate

^{1}H NMR data: 1.25 (d+t, 6H);
1.4 - 2.4 (m, 8H);
2.4 - 3.8 (m, 6H);
4.2 (q, 2H);
4.3 - 4.8 (m, 1H);
5.2 (s, 2H);
7.2 (s, 5H);
7.4 - 8.0 (m, 5H).

Example 28

Benzyl N-(1S-carboethoxy-3-phenyl-3-oxopropyl)-S-alanyl-2β,3aβ,8aβ-decahydrocyclohepta[b]pyrrole-2-carboxylate

^{1}H NMR data: 1.2 (d, 3H);
1.3 (t, 3H);
1.4 - 2.5 (m, 12H);
2.4 - 3.8 (m, 6H);
4.2 (q, 2H);
4.3 - 4.8 (m, 1H);
5.2 (s, 2H);
7.2 (s, 5H);
7.4 - 8.0 (m, 5H).

Example 29

N-(1S-Carboethoxy-3-phenyl-3-oxopropyl)-S-alanyl-2β,3aβ,7aβ-octahydroindole-2-carboxylic acid trifluoroacetate

2.6 g of the mixture of diastereomers from Example 23 were stirred in 15 ml of trifluoroacetic acid at 20 to 25°C for 2 hours. The solution was concentrated in vacuo, the residue was triturated with diisopropyl ether and

filtered off with suction.
Yield: 0.8 g

^{1}H NMR data: 1.2 (d+t, 6H);
1.3 - 3.6 (m, 16H);
4.2 (q, 2H);
4.1 - 4.6 (m, 4H);
7.3 - 8.1 (m, 5H).

Example 30

N-(1S-Carboethoxy-3-phenyl-3-oxopropyl)-S-alanyl-2β,3aβ,6aβ-octahydrocyclopenta[b]pyrrole-2-carboxylic acid trifluoroacetate

This compound was prepared in analogy to the procedure described in Example 29.

^{1}H NMR data: 1.2 (d+t, 6H);
1.3 - 3.6 (m, 14H);
4.15 (q, 2H);
4.0 - 4.6 (m, 4H);
7.3 - 8.0 (m, 5H).

Example 31

N-(1S-Carboethoxy-3-phenyl-3-oxopropyl)-S-alanyl-2β,3aβ,8aβ-decahydrocyclohepta[b]pyrrole-2-carboxylic acid

1 g of tert.-butyl N-(1S-carboethoxy-3-phenyl-3-oxopropyl)-S-alanyl-2β,3aβ,8aβ-decahydrocyclohepta[b]-pyrrole-2-carboxylate was dissolved in 10 ml of methylene chloride, the solution was saturated with hydrogen chloride gas and allowed to stand at 20 to 25°C for 16 hours. The solution was concentrated in vacuo and the residue was triturated with diisopropyl ether and filtered with suction. Yield: 0.4 g

^{1}H NMR data: 1.3 (d+t, 6H);
1.3 - 3.8 (m, 18H);
4.2 (q, 2H);
4.0 - 4.7 (m, 4H);
7.2 - 8.1 (m, 5H).

The carboxylic acids described in the foregoing Examples 29 to 31 can also be prepared from the corresponding benzyl esters by catalytic hydrogenolysis (10% palladium on charcoal, ethanol, 20 to 25°C).

Example 32

N-(1S-Carboxy-3-phenyl-3-oxopropyl)-S-alanyl-2β,3aβ,7aβ-octahydroindole-2-carboxylic acid

For the preparation of this compound, 1 g of N-(1S-carboethoxy-3-phenyl-3-oxopropyl)-S-alanyl-2β,3aβ,7aβ-octahydroindole-2-carboxylic acid was reacted with potassium hydroxide in analogy to the procedure described in Example 19.

^{1}H NMR data: 1.2 (d, 3H);
1.3 - 3.6 (m, 16H);
4.1 - 4.7 (m, 4H);
7.2 - 8.1 (m, 5H).

Example 33

N-(1S-Carboethoxy-3-phenyl-3-hydroxypropyl)-S-alanyl-2β,3aβ,7aβ-octahydroindole-2-carboxylic acid

1 g of N-(1S-carboethoxy-3-phenyl-3-oxopropyl)-S-alanyl-2β,3aβ,7aβ-octahydroindole-2-carboxylic acid was dissolved in 50 ml of anhydrous ethanol and hydrogenated with 1 mole-equivalent of hydrogen and 50 mg of palladium/charcoal at 20 to 25°C under atmospheric pressure. After removal of the catalyst by filtration, the solution was evaporated and the residue was

triturated with diisopropyl ether and filtered off with suction.
Yield: 0.7 g.

^{1}H NMR data: 1.2 (d, 3H);
1.3 (t, 3H);
1.3 - 3.8 (m, 16H);
4.2 (q, 2H);
4.1 - 4.6 (m, 4H);
4.7 (d, 1H);
7.1 - 7.4 (m, 5H).

Example 34

N-(1S-Carboethoxy-3-phenyl-3-hydroxypropyl)-S-alanyl-2β,3aβ,6aβ-octahydrocyclopenta[b]pyrrole-2-carboxylic acid

This compound was prepared according to the procedure described in Example 33 from the compound described in Example 29.

^{1}H NMR data: 1.2 (d, 3H);
1.3 (t, 3H);
1.4 - 3.9 (m, 14H);
4.2 (q, 2H);
4.1 - 4.7 (m, 4H);
4.7 (d, 1H);
7.1 - 7.4 (m, 5H).

Example 35

N-(1S-Carboethoxy-3-phenyl-3-hydroxypropyl)-S-alanyl-2β,3aβ,8aβ-decahydrocyclohepta[b]pyrrole-2-carboxylic acid

This compound was prepared according to the procedure described in Example 33 from the compound described in Example 31.

^{1}H NMR data: 1.25 (d+t, 6H);
1.3 - 4.0 (m, 18H);
4.2 (q, 2H);
4.1 - 4.6 (m, 4H);
4.8 (d, 1H);
7.0 - 7.5 (m, 5H).

Example 36

Benzyl S-alanyl-2S,3aR,7aR-octahydroindole-2-carboxylate

a) Benzyl N-tert.-butoxycarbonyl-S-alanyl-2S,3aR,7aR-octahydroindole-2-carboxylate

13 ml of N-ethylmorpholine, 13.5 g of 1-hydroxybenzotriazole and 29.6 g of benzyl 2β,3aβ,7aβ-octahydroindole-2-carboxylate hydrochloride were added to a solution of 19 g of Boc-Ala-OH in 100 ml of DMF. The mixture was cooled in an ice bath and 21 g of dicyclohexylcarbodiimide were added. The mixture was stirred at 20 to 25°C for 15 hours. The precipitated urea was filtered off with suction, the filtrate was evaporated in vacuo and taken up in ethyl acetate. The organic phase was extracted 3 times in each case with aqueous potassium bisulfate, potassium bicarbonate and sodium chloride, dried and concentrated. The residue was chromatographed on silica gel with ethyl acetate/cyclohexane (1:3). The first fraction contained the desired product. Yield: 21 g

^{1}H NMR data: 1.3 (d, 3H);
1.45 (s, 9H);
1.1 - 2.4 (m, 12H);
3.2 - 3.9 (m, 2H);
5.3 (s, 2H);
7.4 (s, 5H).

b) Benzyl S-alanyl-2S,3aR,7aR-octahydroindole-2-carboxylate

20.5 g of benzyl N-tert.-butoxycarbonyl-S-alanyl-2S,3aR,7aR,octahydroindole-2-carboxylate were dissolved in 50 ml of trifluoroacetic acid. After a reaction time of 10 min, the solution was concentrated in vacuo, and the residue was triturated several times with diisopropyl ether and then dried in vacuo. Yield 14 g.

Examples 37 and 38:

These compounds were prepared in analogy to the procedures described in Example 36 under a) and b).

Example 37

Benzyl S-alanyl-2S,3aR,6aR-octahydrocyclopenta[b]pyrrole-2-carboxylate

^{1}H NMR data: 1.3 (d, 3H);
1.1 - 2.4 (m, 10H);
3.2 - 3.9 (m, 2H);
5.2 (s, 2H);
7.4 (s, 5H).

Example 38

Benzyl S-alanyl-2S,3aR,8aR-decahydrocyclohepta[b]pyrrole-2-carboxylate

^{1}H NMR data: 1.3 (d, 3H);
1.1 - 2.4 (m, 14H);
3.2 - 3.9 (m, 2H);
5.2 (s, 2H);
7.4 (s, 5H).

Example 39

N-(1S-Carboethoxy-3-phenylpropyl)-S-alanyl-2S,3aR,7aR-octahydroindole-2-carboxylic acid

a) Benzyl N-(1S-carboethoxy-3-phenylpropyl)-S-alanyl-2S,3aR,7aR-octahydroindole-2-carboxylate

10 mmoles of benzyl S-alanyl-2S,3aR,7aR-octahydroindole-2-carboxylate were dissolved in 30 ml of anhydrous ethanol. The solution was adjusted to a pH of 7.0 by means of ethanolic potassium hydroxide and 1 g of powdered molecular sieve (4Å) and then 10 mmoles of ethyl 2-keto-4-phenylbutyrate were added. A solution of 1 g of sodium cyanoborohydride in 10 ml of anhydrous ethanol was slowly added dropwise. After a reaction time of 20 hours at 20 to 25°C, the reaction solution was filtered and the solvent was distilled off. The residue was taken up in ethyl acetate/water. After concentration of the ethyl acetate phase, the residue was chromatographed on silica gel with ethyl acetate/cyclohexane (1:4). The ^{1}H NMR data agree with the data of the compound from Example 11.

b) The compound obtained above was reacted further as described in Example 17, method A to give the desired compound.

Example 40

Benzyl N-(1S-carboethoxy-3-oxo-3-phenylpropyl)-S-alanyl-2β,3aβ,6aβ-octahydrocyclopenta[b]pyrrole-2-carboxylate

10 mmoles of benzyl S-alanyl-2S,3aR,6aR-octahydrocyclopenta[b]pyrrole-2-carboxylate were dissolved in 100 ml of anhydrous ethanol together with 10 mmoles of ethyl 3-benzoylacrylate and 10 mmoles of triethylamine and the mixture was stirred at 20 to 25°C for 24 hours. It was

then neutralized with 1 N hydrochloric acid, evaporated to dryness and the residue was taken up with ethyl acetate/water. The ethyl acetate phase was dried, evaporated and chromatographed on silica gel.

Example 41

Benzyl N-(1S-carboethoxy-3-oxo-3-phenylpropyl)-S-alanyl-2β,3aβ,8aβ-decyhydrocyclopenta[b]pyrrole-2-carboxylate (sic)

10 mmoles of acetophenone, 10 mmoles of ethyl glyoxylate and 10 mmoles of benzyl S-alanyl-2S,3aR,8aR-decahydrocyclohepta[b]pyrrole-2-carboxylate were heated at 45°C in 30 ml of glacial acetic acid for 36 hours. After concentration in vacuo, the mixture was made alkaline with aqueous sodium bicarbonate and extracted with ethyl acetate. The ethyl acetate phase was concentrated and chromatographed on silica gel.

Example 42

Benzyl N-(1S-carboethoxy-3-phenylpropyl)-S-alanyl-2S,3aR,7aS-octahydroindole-2-carboxylate

a) Benzyl DL-2β,3aβ,7aα-octahydroindole-2-carboxylate hydrochloride

1.4 g of DL-2β,3aβ,7aα-octahydroindole-2-carboxylic acid were added, at -10° to 0°C, to a solution of 1.4 ml of thionyl chloride in 14 ml of benzyl alcohol prepared at -5 to 0°C. The mixture was stirred at 0°C for 1 hour and was then allowed to stand overnight at 20 to 25°C. The benzyl alcohol was distilled off at 50°C under high vacuum and the residue was digested with diisopropyl ether. 2.5 g of colorless crystals, of m.p. 154°C, were obtained.

b) Benzyl N-(1S-carboethoxy-3-phenylpropyl)-S-alanyl-2β,3aβ,7aα octahydroindole-2-carboxylate

1.06 g of 1-hydroxybenzotriazole, 2.2 g of benzyl DL-2β,3aβ,7aα-octahydroindole-2-carboxylate hydrochloride and 1.08 ml of N-ethylmorpholine were added to a suspension of 2.16 g of N-(1S-carboethoxy-3-phenylpropyl)-S-alanine in 8.6 ml of anhydrous dimethylformamide and then 1.7 g of dicyclohexylcarbodiimide were added at 0°C. After stirring at 20 to 25°C for 3.5 hours, the reaction mixture was diluted with 20 ml of ethyl acetate and the precipitated dicyclohexylurea was filtered off. After concentration in vacuo, the residue was taken up in ether, washed twice with saturated aqueous sodium bicarbonate, dried over sodium sulfate and evaporated. After chromatography on silica gel using ethyl acetate-cyclohexane as the mobile phase, 2 pale yellow oils were obtained in the ratio 1:1, and these each contain one isomer of the desired compound.

^{1}H NMR data of the isomer having the 2R,3aR,7aS configuration:

7.35 (s, 5H);
7.2 (s, 5H);
5.18 (s, 2H);
4.55 (d, 1H);
4.1 (q, 2H);
3.4 - 2.3 (m, 6H);
2.4 - 1.3 (m, 12H);
1.3 (t, 3H);
1.1 (d, 3H).

^{1}H NMR data of the isomer having the 2S,3aS,7aR configuration:

7.35 (s, 5H);
7.2 (s, 5H);
5.16 (s, 2H);
4.9 - 4.2 (m, 1H);

4.2 (q, 2H);
3.9 - 2.4 (m, 6H);
2.4 - 1.4 (m, 12H);
1.25 (d+t, 6H).

c) N-(1S-carboethoxy-3-phenylpropyl)-S-alanyl-2S,3aR,7aS-octahydroindole-2-carboxylic acid (reference example)

1.7 g of the isomer having the 2S,3aS,7aR configuration obtained under b) were hydrogenated under atmospheric pressure in 60 ml of anhydrous ethanol with the addition of 200 mg of palladium-charcoal (10%) at 20 to 25°C for 2 hours. The catalyst was filtered off and the filtrate was evaporated. 1.2 g of the title compound were obtained as a colorless foam.

^{1}H NMR data: 7.2 (s, 5H);
4.4 (m, 4H);
4.2 (q, 2H);
3.6 - 1.3 (m, 18H);
1.28 (d+t, 6H).

The hydrochloride of the abovementioned compound was obtained as a colorless amorphous powder.

Example 43 (reference example)

2β,3aα,7aβ-Octahydroindole-2-carboxylic acid

a) 3,4,5,6,7,8-Octahydro-1H-quinolin-2one (sic)

392 g of cyclohexanone and 212 g of acrylonitrile, together with 20 g of cyclohexylamine, 4 g of glacial acetic acid and 0.4 g of hydroquinone, were heated under reflux for 4 hours up to a final temperature of 200°C. The distillate obtained after distillation at 100 to 150°C/0.5 mm Hg was heated with 10 ml of 50% strength acetic acid at 200°C for 2 days. After cooling down, the reaction mixture was recrystallized

from methanol/water. Combined with the residue from distillation, obtained previously, which was recrystallized from n-hexane, 460 g of the product of m.p. 143 to 144°C were obtained.

b) Trans-octahydro-1H-quinolin-2one (sic)

A mixture of 25 g of the product obtained under a) and 70 g of sodium formate in 120 ml of formic acid was heated to boiling under reflux for 18 hours. The reaction solution was made alkaline with 20% strength aqueous sodium hydroxide and extracted with ethyl acetate. The organic phase was dried over sodium sulfate and concentrated. The residue was recrystallized from cyclohexane and the product was obtained having an m.p. of 152°C.

c) 3,3-Dichloro-trans-octahydro-1H-quinolin-2one (sic)

A solution of 36.4 g of sulfuryl chloride in 40 ml of chloroform was added dropwise at 20 to 30°C over 30 minutes to a solution of 19.4 g of the compound obtained under b) and 24.3 g of phosphorus pentachloride in 300 ml of anhydrous chloroform. The mixture was heated to boiling for 6 hours and allowed to stand overnight at 20 to 25°C.

The mixture was neutralized with ice-cold saturated aqueous potassium carbonate, extracted with methylene chloride, and the organic phase was dried over sodium sulfate and then concentrated. After recrystallization of the residue from ethanol, with the addition of active charcoal, 25 g of the product, of m.p. 195 to 198°C, were obtained.

d) 3-Chloro-trans-octahydro-1H-quinolin-2one (sic)

15.6 g of the compound obtained under c) were hydrogenated under atmospheric pressure in 1 l of ethanol

and 9.7 ml of triethylamine, with the addition of Raney nickel, at 20 to 25°C until 1 mole-equivalent of hydrogen had been taken up.

After the catalyst had been filtered off, the filtrate was evaporated to dryness and the residue was taken up in ethyl acetate. The organic phase was washed twice with water, dried over sodium sulfate and concentrated. The residue was triturated with diisopropyl ether, filtered off with suction and dried. The product was obtained in the form of pale yellow crystals of m.p. 115 - 120°C.

e) 2β,3aα,7aβ-Octahydroindole-2-carboxylic acid

3.75 g of the compound obtained under d) were added to a boiling solution of 6.63 g of barium hydroxide octahydrate in 120 ml of water. After heating under reflux for 4 hours, 0.9 ml of concentrated sulfuric acid were added, heating under reflux was continued a further hour, the reaction solution was filtered and the filtrate was adjusted to a pH of 6.5 with 1 N sodium hydroxide. After evaporation of the solution, the residue was heated in ethanol, again filtered and the filtrate was evaporated to a small volume. On cooling down, a crystalline 1:1 mixture of the title compound with 2β,3aβ,7aα-octahydroindole-2-carboxylic acid of m.p. 275-276°C was obtained.

Example 44 (reference example)

2β,3aβ,6aα-Octahydrocyclopenta[b]pyrrole-2-carboxylic acid

a) 1,2,3,4,6,7-Hexahydro-5H-1-pyrind-2-one

A mixture of 1 mole of cyclopentanone, 1 mole of acrylonitrile, 0.05 mole of ammonium acetate and 3 ml

of 30% strength ammonia was heated in a pressure vessel for 3 hours at 220°C. The mixture was filtered through silica gel with ethyl acetate/cyclohexane (1:1) and the residue obtained after evaporation of the filtrate was recrystallized from cyclohexane. The product melted at 118 to 120°C.

^{1}H NMR data: 9.4 (broad s, 1H);
3.2 - 2.0 (m, 12H).

b) Octahydro-trans-5H-1-pyrind-2-one

This compound was prepared in analogy to the procedure described in Example 43 under b).

^{1}H NMR data: 7.8 (broad s, 1H);
2.9 (broad s, 1H);
2.6 - 2.2 (m, 2H);
2.1 - 1.0 (m, 8H).

c) 3,3-Dichlorooctahydro-trans-5H-1-pyrind-2-one

This compound was prepared in analogy to the procedure described in Example 43 under c).

^{1}H NMR data: 7.9 (broad s, 1H);
3.8 (broad s, 1H);
3.2 - 2.0 (m, 2H);
2.1 - 1.0 (m, 6H).

d) 3-Chlorooctahydro-trans-5H-1-pyrind-2-one

This compound was prepared in analogy to the procedure described in Example 43 under d).

^{1}H NMR data: 7.8 (broad s, 1H);
4.6 - 4.3 (m, 1H);
3.3 - 3.0 (m, 1H);
2.1 (d, J = 6 Hz, 2H);

1.8 - 1.1 (m, 6H).

e) 2β,3aβ,6aα-Octahydrocyclopenta[b]pyrrole-2-carboxylic acid

This compound was prepared in analogy to the procedure described in Example 43 under e).

^{1}H NMR data: 4.7 - 4.4 (m, 1H);
3.0 - 0.9 (m, 10H).

Example 45

N-(1-S-Carboethoxy-3-phenylpropyl)-O-ethyl-S-tyrosyl-2S,3aR,7aS-octahydroindole-2-carboxylic acid

a) N-(1-R,S-Carboethoxy-3-phenylpropyl)-O-ethyl-S-tyrosyl (sic) benzyl ester

24 g of ethyl benzoyl acrylate in 100 ml of ethanol were reacted with 30 g of O-ethyl-S-tyrosine benzyl ester in the presence of 0.5 ml of triethylamine and, after the solution had been concentrated and the residue had been digested with diethyl ester (sic)/petroleum ether (1:1) and dried in vacuo, 42 g of the title compound were obtained.

b) N-(1-R,S-Carboethoxy-3-phenylpropyl)-O-ethyl-S-tyrosine

40 g of the compound obtained in Example 45a were hydrogenated in 800 ml of glacial acetic acid with 4 g of Pd/C (10%) under 100 bar and at room temperature. Chromatography on silica gel with ethyl acetate/cyclohexane (1:3) as mobile phase and drying of the residue from evaporation resulted in 25 g of the title compound which was almost pure by thin-layer chromatography, m.p. 205-213°C

$C_{23}H_{29}NO_5$ (399.5) Calc. C 69.15 H 7.31 N 3.50
Found C 69.5 H 7.4 N 3.3

c) N-(1-S-Carboethoxy-3-phenylpropyl)-O-ethyl-S-tyrosyl-2S,3aR,7aS-octahydroindole-2-carboxylic acid

1.5 g of the benzyl ester described in Example 42a were reacted in analogy to the procedure described in Example 45b with 2.5 (sic) of N-(1-R,S-carboethoxy-3-phenylpropyl)-O-ethyl-S-tyrosine, 1.3 (sic) dicyclohexylcarbodiimide and 0.8 g of 1-hydroxybenzotriazole. Chromatography of the crude product on silica gel with cyclohexane/ethyl acetate (1:1) as mobile phase yielded 1 g of the title compound as a colorless oil.

The ^{1}H NMR data and the mass spectrum are consistent with the stated structure.

The benzyl ester was hydrogenolyzed in analogy to the procedure described in Example 42c. 0.6 g of the title compound was obtained as a colorless amorphous powder.

^{1}H NMR data: 7.3 (s, 5H);
7.1 - 6.5 (2d, 4H);
4.4 - 4.0 (m, 4H);
3.9 - 3.0 (m, 4H);
2.9 - 1.2 (m, 17H);
1.4 (t, 3H);
1.25 (t, 3H).

Example 46

N-(1-S-Carboethoxy-3-phenylpropyl)-O-methyl-S-tyrosyl-2S,3aR,7aS-octahydroindole-2-carboxylic acid

The title compound was obtained in analogy to the procedure described in Example 45 by using O-methyl-tyrosine benzyl ester instead of O-ethyl-tyrosine benzyl ester in the stage analogous to 45a.

^{1}H NMR data: 7.2 (s, 5H);
7.1 - 6.5 (2d, 4H);
4.4 - 4.0 (m, 3H);
3.9 - 3.0 (m, 3H);
3.5 (s, 3H);
2.9 - 1.2 (m, 17H);
1.3 (t, 3H).

Example 47

N-(1-S-Carboethoxy-3-phenylpropyl)-O-ethyl-S-tyrosyl-2S,3aS,7aR-octahydroindole-2-carboxylic acid

Prepared from the amino acid described in Example 43 in analogy to the procedure described in Example 45. The ^{1}H NMR data are consistent with the stated structure.

Example 48

N-(1-S-Carboethoxy-3-phenylpropyl)-O-methyl-S-tyrosyl-2S,3aS,7aR-octahydroindole-2-carboxylic acid

Prepared in analogy to the procedure described in Example 46 by using the amino acid described in Example 43. The ^{1}H NMR data are consistent with the stated structure.

Example 49

N-(1-S-carboethoxy-3-phenylpropyl)-O-ethyl-S-tyrosyl-2S,3aR,6aS-octahydrocyclopenta[b]pyrrole-2-carboxylic acid

Prepared in analogy to the procedure described in Example 45 by using the amino acid described in Example 44.

^{1}H NMR data: 7.3 (s, 5H);
7.2 - 6.6 (2d, 4H);
4.4 - 3.9 (m, 4H);
3.9 - 3.0 (m, 4H);

2.9 - 1.2 (m, 15H);
1.35 (t, 3H);
1.25 (t, 3H).

Example 50

N-(1-S-Carboethoxy-3-phenylpropyl)-O-methyl-S-tyrosyl-2S,3aR,6aS-octahydrocyclopenta[b]-2-carboxylic acid (sic)

Prepared in analogy to the procedure described in Example 46 by using the amino acid described in Example 44. The ^{1}H NMR data are consistent with the stated structure.

Example 51

N-(1-S-Carboethoxy-3-phenylpropyl)-O-ethyl-S-tyrosyl-2S,3aS,6aR-octahydrocyclopenta[b]pyrrole-2-carboxylic acid

Prepared in analogy to the procedure described in Example 45. The analytical data are consistent with the stated structure.

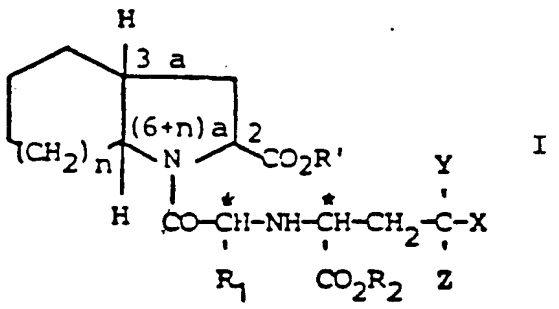
Example 52

N-(1-S-Carboethoxy-3-phenylpropyl)-O-methyl-S-tyrosyl-2S,3aS,6aR-octahydrocyclopenta[b]-2-carboxylic acid (sic)

Prepared in analogy to the procedure described in Example 46. The analytical data are consistent with the stated structure.

Patent claims for the contracting states BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. A compound of the formula I



I

in which the hydrogen atoms on the bridgehead carbon atoms 3a and (6 + n)a have the cis or trans configuration relative to one another, wherein, in the case of the cis configuration, the carboxyl group on carbon atom 2 is oriented exo to the bicyclic ring system and wherein

n denotes 0, 1 or 2,

R_1 denotes hydrogen, (C_1-C_6)-alkyl which can optionally be substituted by amino, (C_1-C_4)-acylamino or benzoylamino, (C_2-C_6)-alkenyl, (C_5-C_9)-cycloalkyl, (C_5-C_9)-cycloalkenyl, (C_5-C_7)-cycloalkyl-(C_1-C_4)-alkyl, aryl or partially hydrogenated aryl, which can, in each case, be substituted by (C_1-C_4)-alkyl, (C_1-C_2)-alkoxy or halogen, aryl-(C_1-C_4)-alkyl, which can be substituted as defined previously in the aryl radical, a monocyclic or bicyclic heterocyclic radical having 5 to 7 or 8 to 10 ring atoms respectively, of which 1 to 2 ring atoms are sulfur or oxygen atoms and/or of which 1 to 4 ring atoms are nitrogen atoms, or a side chain of a naturally occurring amino acid,

R_2 denotes hydrogen, (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl or aryl-(C_1-C_4)-alkyl,

R' denotes hydrogen, benzyl or tert. butyl,

Y denotes hydrogen or hydroxyl,

Z denotes hydrogen or

Y and Z together denote oxygen,

X denotes (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl, (C_5-C_9)-cycloalkyl, aryl which can be mono-, di- or tri-substituted

by (C_1-C_4)-alkyl, (C_1-C_4)-alkoxy, hydroxyl, halogen, nitro, amino, (C_1-C_4)-alkylamino, di-(C_1-C_4)-alkylamino or methylenedioxy, or indol-3-yl, and aryl denotes phenyl or naphthyl, and the physiologically acceptable salts thereof, excluding compounds of the formula 1 (sic) in which the hydrogen atoms on the bridgehead carbon atoms 3a and (6+n)a have the trans configuration relative to one another and wherein

R_1 denotes methyl,

R_2 denotes hydrogen, (C_1-C_4)-alkyl or benzyl,

R' denotes hydrogen and

X denotes phenyl and

n, Y and Z are as defined above, as well as the salts thereof.

2. A compound of the formula I as claimed in claim 1, wherein the hydrogen atoms on the bridgehead carbon atoms 3a and (6+n)a have the trans configuration relative to one another.

3. A compound of the formula I as claimed in claim 1, wherein the hydrogen atoms on the bridgehead carbon atoms 3a and (6+n)a have the cis configuration relative to one another and the carboxyl group on carbon atom 2 is oriented exo to the bicyclic ring system.

4. A compound of the formula I as claimed in any of claims 1 to 3, wherein the carbon atom in position 2 of the bicyclic ring system and the carbon atoms labeled with an asterisk in the side chain have the S configuration.

5. A compound of the formula I as claimed in any of claims 1 to 4, wherein

R_1 denotes hydrogen, (C_1-C_3)-alkyl, (C_2-C_3)-alkenyl, benzyl or 4-aminobutyl,

R_2 denotes hydrogen, (C_1-C_4)-alkyl or benzyl and

X denotes phenyl, which can be mono- or di-substituted, or, in the case of methoxy, tri-substituted by (C_1-C_2)-alkyl, (C_1-C_2)-alkoxy, hydroxyl, fluorine, chlorine,

bromine, amino, (C_1-C_4)-alkylamino, di-(C_1-C_4)-alkylamino, nitro or methylenedioxy.

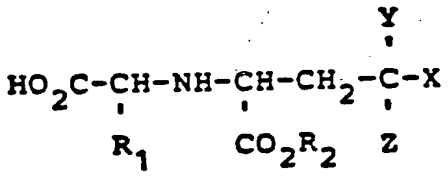
6. A compound of the formula I as claimed in any of claims 1 to 5, wherein R_1 denotes methyl and X denotes phenyl.

7. A compound of the formula I as claimed in any of claims 1 to 6, wherein
R_2 denotes hydrogen or ethyl.

8. A compound of the formula I as claimed in any of claims 1 to 7, wherein R' denotes hydrogen.

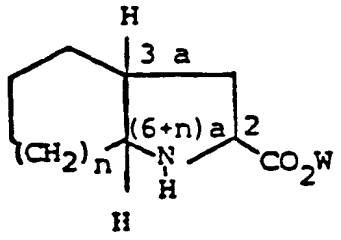
9. N-(1-S-Carboethoxy-3-phenyl-propyl)-S-alanyl-2S,3aR,7aR-octahydroindole-2-carboxylic acid and the physiologically acceptable salts thereof.

10. A process for the preparation of the compounds of the formula I as claimed in any of claims 1 to 9, which
a) comprises reacting a compound of the formula II



II

wherein R_1, R_2, X, Y and Z have the meanings as in formula I, with a compound of the formula III



III

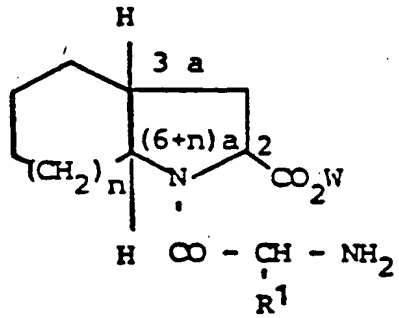
in which the hydrogen atoms on the carbon atoms 3a and (6+n)a have the cis or trans configuration relative to one another, wherein, in the case of the cis configuration, the group $-CO_2W$ is oriented exo to the bicyclic ring system and wherein
n denotes 0, 1 or 2 and
W denotes a radical which can be cleaved off by

hydrogenolysis or by acid, and subsequently cleaving off, if appropriate, the radical W and, if appropriate, the radical R_2 to form the free carboxyl group(s),

or

b) for the preparation of compounds of the formula I in which Y and Z together denote oxygen, comprises

b_1) reacting a compound of the formula IV



IV

in which the hydrogen atoms on the carbon atoms 3a and (6+n)a have the cis or trans configuration relative to one another, wherein, in the case of the cis configuration, the group $-CO_2W$ is oriented exo to the bicyclic ring system, and wherein n and R_1 have the meanings as in formula I and W has the meaning as in formula III, with a compound of the formula V,

$$R_2O_2C\text{-}CH{=}CH\text{-}CO\text{-}X \qquad V$$

wherein R_2 and X have the meanings as in formula I, and subsequently cleaving off, if appropriate, the radical W and, if appropriate, also the radical R_2 to form the free carboxyl group(s), or

b_2) reacting a compound of the formula IV mentioned under b_1) with a compound of the general formula VI wherein R_2 has the meaning as in formula I, and with a compound of the general formula VII

$$OHC\text{-}CO_2R_2 \qquad X\text{-}CO\text{-}CH_3$$

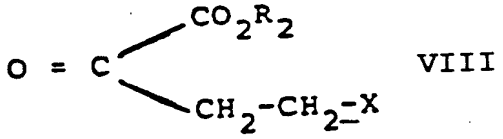
VI VII

wherein X has the meaning as in formula I, and subsequently cleaving off, if appropriate, the

radical W and, if appropriate, the radical R_2 to form the free carboxyl group(s), or

c) for the preparation of compounds of the formula I in which Y and Z each denote hydrogen, comprises

c_1) reacting a compound of the formula IV mentioned under b_1) with a compound of the formula VIII



VIII

wherein R_2 and X have the meanings as in formula I, reducing the Schiff's bases obtained and subsequently cleaving off, if appropriate, the radical W and, if appropriate, the radical R_2 to form the free carboxyl group(s), or

c_2) catalytically reducing with hydrogen a compound of the formula I in which Y and Z together denote oxygen,

or

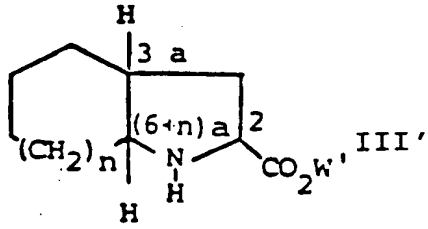
d) for the preparation of compounds of the formula I in which Y denotes hydroxyl and Z denotes hydrogen, comprises reducing a compound of the formula I in which Y and Z together denote oxygen, catalytically with hydrogen or with a reducing agent, such as sodium borohydride, and converting the compounds obtained as in (a) - (d), if appropriate, into the physiologically tolerated salts thereof.

11. A compound as claimed in any of claims 1 to 9 for use as a medicine.

12. A compound as claimed in claim 11 for use as a medicine for the treatment of high blood pressure.

13. A compound as claimed in claim 11 or 12 for use in combination with a diuretic.

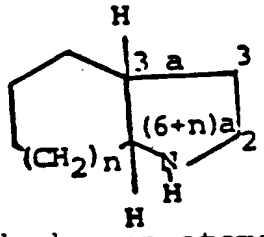
14. A compound of the formula III'



III'

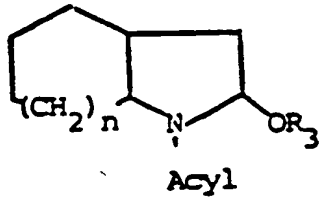
in which the hydrogen atoms on the carbon atoms 3a and (6+n)a have the cis configuration relative to one another, and the group $-CO_2W'$ on carbon atom 2 is oriented exo to the bicyclic ring system and wherein
n denotes 0, 1 or 2 and
W' denotes hydrogen, (C_1-C_{18})-alkyl or (C_7-C_{10})-aralkyl.

15. A process for the preparation of the compounds of the formula III' as claimed in claim 14 which comprises
a) acylating a compound of the formula IX



IX

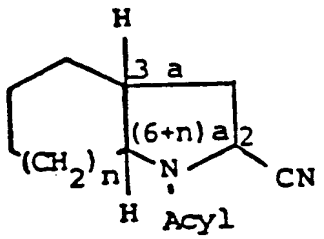
wherein the hydrogen atoms on the carbon atoms 3a and (6+n)a have the cis configuration relative to one another and wherein n denotes the number 0, 1 or 2, subsequently anodically oxidizing the compound obtained with an aliphatic alcohol in the presence of a conducting salt to give a compound of the formula X



X

wherein n has the abovementioned meaning, acyl is an aliphatic or aromatic acyl radical, and R_3 denotes (C_1-C_4)-alkyl, reacting this product with trimethylsilyl cyanide in an aprotic organic solvent in the presence of a Lewis acid to give a compound of the

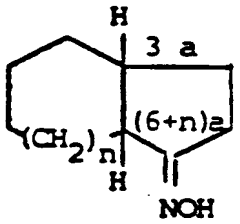
formula XI



XI

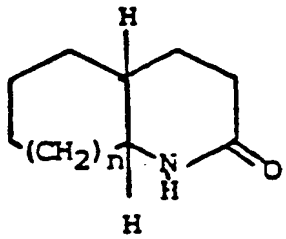
wherein the hydrogen atoms on the carbon atoms 3a and (6+n)a have the cis configuration relative to one another and the group -CN is oriented exo to the bicyclic ring system and wherein n has the above-mentioned meaning, and hydrolyzing the latter by the action of acids or bases to give a compound of the formula III' with W' = hydrogen and if appropriate esterifying the latter, or

b) reacting a compound of the formula XII



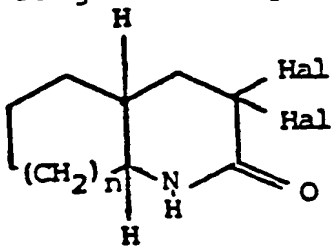
XII

wherein the hydrogen atoms on the carbon atoms 3a and (6+n)a have the cis configuration and n has the abovementioned meaning, in a Beckmann rearrangement to give a compound of the formula XIII



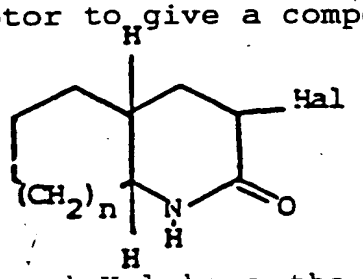
XIII

wherein n has the abovementioned meaning, halogenating the latter to give a compound of the formula XIV,



XIV

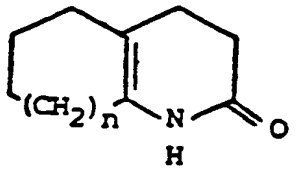
wherein n has the abovementioned meaning and Hal denotes a halogen atom, catalytically reducing the latter in a polar protic solvent with addition of an acid acceptor to give a compound of the formula XV



XV

wherein n and Hal have the abovementioned meanings, and subsequently reacting the latter in an alcoholic solvent under the action of a base to give a compound of the formula III' with W' = hydrogen and optionally esterifying the latter, or

c) reducing, under metal catalysis in a protic medium, a compound of the formula XVI



XVI

wherein n has the abovementioned meaning, to give a compound of the formula XIII mentioned under b), and further reacting the latter as described under b), or if appropriate hydrolyzing resulting esters of the formula III' and, if W' is hydrogen, if appropriate esterifying to compounds of the formula III' in which W' represents alkyl with 1 to 18 carbon atoms or aralkyl with 7 to 10 carbon atoms.

16. A pharmaceutical agent containing a compound as claimed in any of claims 1 to 9.

17. An agent as claimed in claim 16, which additionally contains a diuretic.

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